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10/542,284	11/15/2006	John Erwin Farley	AM100238	3032

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WYETH
PATENT LAW GROUP
5 GIRALDA FARMS
MADISON, NJ 07940

EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,284	FARLEY ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,12-23,25,26 and 29-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,12-23,25,26 and 29-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 9/22/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-23 and 25-39, and SEQ ID NO: 1 with its corresponding amino acid SEQ ID NO: 2, in the reply filed on 5/4/09 is acknowledged. **NOTE:** It was discovered that claims 27 and 28 were inadvertently placed in Group I; however they are drawn to polypeptides which are part of Group II. Claims 27 and 28 have been placed in Group II.

Claims 4-11 (drawn to non-elected sequences), 24, 27, 28 and 40-103 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-3, 12-23 and 25, 26 and 29-39 are currently under examination.

Applicants stated in the first line on page 4 of the response submitted 5/4/09 that the election was being made **without** traverse. However, Applicants do recite that they feel that Groups 2, 4, 6, 8, 10, 12, 13 and 16 comprise a special technical feature, the PorA protein. This has been fully and carefully considered but is not deemed persuasive. Group I is drawn to a method 'for increasing expression levels of a PorA protein' and is *not* drawn to a product. Further, the Inventions of Groups I-23 do not contain the same special technical feature as they contain completely separate methods and/or products which are biogically, structurally and chemically distinct products. Additionally, there are patentably distinct products contained ***within*** many of these three groups, e.g., nucleotide sequences encoding different proteins (as well as proteins comprising different amino acid sequences/encoded by different nucleic acid sequences) are structurally distinct chemical compounds and are different special technical features. Examination will be restricted to only the elected sequence. It is additionally noted that this sequence election requirement is a restriction requirement and not a species election requirement.

Claim Objections

2. Claims 1, 12-23, 25, 26 and 29-39 are objected to because of the following informalities: they contain non-elected subject matter which must be removed from the claims, e.g., non-elected SEQ ID NOs.. Appropriate correction is required.

Claim Rejections - 35 USC § 112-2nd paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-3, 12-23 and 25, 26 and 29-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 12, 26, 29 and 30 are vague and indefinite due to the phrase 'codon 18' which amino acid residues of SEQ ID NO: 1 does this 'codon' represent. Clarification and/or correction is requested.

Claim 1 is also vague and indefinite because it recites a 'method for increasing the levels of a Neisseria PorA protein or polypeptide in a host cell' yet there do not appear to be any active steps for increasing the expression. The method steps appear to be like any other recombinant expression method. It appears codon 18 has been mutated in order to cause this increased expression, but there is nothing in the claim that states this. Clarification and/or correction is requested.

Claim 3 recites that the polynucleotide encoding the PorA protein or polypeptide is 'isolated from N.meningitidis'. This is vague and indefinite because it does not appear that the polynucleotide with the mutated codon 18 is naturally occurring. Is this

claim referring to a naturally occurring mutant nucleotide sequence or is it referring to isolating the strain prior to making a mutation at codon 18? This is vague and confusing. Appropriate clarification and/or correction is requested.

Claims 1, 2, and 25 are vague and indefinite due to the phrase "other than an ATC codon' as it is unclear what codons are encompassed in this phrase. The structure referred to is not readily elucidated and the metes and bounds of the invention cannot be understood. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. Clarification and/or correction is requested.

Claim 39 recites the limitation "the polynucleotide" in line 1. There is insufficient antecedent basis for this limitation in the claim because the claim from which it depends, claim 34, does not recite a polynucleotide, but recites 'the vector'. Clarification and/or correction is requested.

Claim Rejections - 35 USC § 112-Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 13-23, 25, 29 and 31-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains

subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a method for increasing the expression levels of a Neisseria PorA protein or polypeptide in a host cell by tranfecting/infecting/transforming a host cell with an expression vector comprising a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 wherein codon 18 is anything but 'ATC'. The breadth of the instant claims is drawn to polynucleotides which are not specified in the sequence disclosure and methods which utilize these polynucleotides to enhance expression levels. The specification states that substitutions, additions, or deletions may be made to the defined sequences; however, the specification provides no guidance as to what nucleic acids may be changed without causing a detrimental effect to the adhesion and penetration protein to be produced. It allows for ***any*** change at codon 18 (anything but 'ATC'). It is unpredictable as to which nucleic/amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. To start with the DNA sequence first, this requires even more work on

the part of the skilled artisan. The instant claims are drawn to nucleic acids comprising a sequence with a given percent similarity to a nucleic acid which encodes a protein. Selective point mutation to one key residue could eliminate the function of the polypeptide. It could eliminate its adhesion and penetration properties. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. Applicants have not shown which nucleotides may be changed without causing a detrimental effect to the protein in which it encodes, nor has it shown which substitutions would allow for increased expression levels. With the exception of 'TAC' at codon 18, Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a single amino acid difference may account for markedly different biological activities. Rudinger et al. (June 1976. Peptide Hormones. Biol.Council. pages 5-7) also teaches that amino acids owe

their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study._Given the lack of guidance contained in the specification regarding acceptable nucleotide substitutions, additions or deletions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112-Written Description

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 1-3, 13-23, 25, 29 and 31-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In 1999, the United States Patent and Trademark Office ("USPTO") published training materials regarding the examination of patent applications under the written description requirement of 35 U.S.C. § 112, first paragraph. (See http ://www.uspto. gov/web/offices/pac/writtende sc.pdf). Since that time, the case law and technology have developed in such a way as to necessitate a revision of the 1999 training materials. Consequently, this 2008 revision was created to supersede

and replace the 1999 training materials. To the extent that any conflict exists between the 1999 training materials and the present materials, the present materials control. The claims have been evaluated with regard to written description based on the Written Description Guidelines and Training Materials published in 2008/

The instant claims are drawn to isolated nucleic acids with an open-ended mutation, e.g., anything but 'ATC' at codon 18 of SEQ ID NO: 1, and methods of using said nucleic acid to increase the expression levels of a Neisseria porA protein or polypeptide. With the exception of 'TAC' at codon 18, the specification has not set forth any other sequences which would provide for the function of increasing expression levels of porA protein. ' To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. Applicants have not described the genus of claimed nucleotides such that the specification might reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed.

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "'Written Description" Requirement (66 FR 1099-1111, January 5,2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings

or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed. The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus'" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan et al (Nature Biotechnology 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Chothia et al (THE EMBO JOURNAL, 1986, 5/4:823-26) also teach that there is a limit to how much substitution can be tolerated before the original tertiary structure is lost. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of fragments or variants of the eleven peptides, the skilled artisan could not

immediately recognize that Applicants were in possession of the claimed genus of peptides at the time of filing.

Therefore, because the art is unpredictable, the claims do not meet the written description guidelines. The scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification does not describe any members of the claimed genus by complete structure. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus, and thus, that the applicant was not in possession of the claimed genus. The claimed subject matter is not supported by an adequate written description because a representative number of species has not been described.

There are no drawings or structural formulas disclosed of any of these fragments or variants of the claimed polynucleotides. There is no teaching in the specification regarding which substitutions will still produce a polypeptide which is expressed at increased levels. Although the disclosure of SEQ ID NO: 1 combined with the knowledge in the art, may put one in possession of polynucleotides that possess 'othter than ATC' at codon 18, the level of skill and knowledge in the art is such that one of ordinary skill would not be able to identify without further testing which of those peptides polynucleotides have the ability when used in a vector and expressed in a host cell, to produce a polypeptide with increased expression levels. Based on the lack of knowledge and predictability in the art, those of ordinary

skill in the art would not conclude that the applicant was in possession of the claimed genus of polynucleotides based on the single species.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to substitutions and their functional abilities of causing increased porA expression 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). With regard to (4) the nature of the invention and (5) the state of the prior art, these have been discussed above. One of skill in the art would require guidance, in order to make or use the polynucleotides in the methods,as instantly claimed.

Sequence Compliance

8. It is noted that Figures 1-3 of the instant specification recites a nucleotide/amino acid sequence which is encompassed by the definitions for nucleotide sequences as set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). The M.P.E.P., Section 2422.02, 37 CFR 1.821(b) requires exclusive conformance, with regard to the manner in which the nucleotide/amino acid sequences are presented and described, with the sequence rules for all applications that include nucleotide sequences that fall within the definitions.

When a sequence is presented in a drawing, regardless of the format or the manner of the presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. It does not appear that the sequence recited in Fig. 2 is in the Sequence Listing. Additionally, Applicants are responsible for meeting compliance with any sequence in the specification the Examiner may have inadvertently missed.

APPLICANT MUST COMPLY WITH THE SEQUENCE RULES WITHIN THE SAME TIME PERIOD AS IS GIVEN FOR RESPONSE TO THIS ACTION, 37 C.F.R. 1.821-25. Failure to comply with these requirements will result in **ABANDONMENT** of the application under 37 C.F.R. 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645